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EXAMINER				
CORDERO GARCIA, MARCELA M				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/551,375

Applicant(s)

EL-RASHIDY, RAGAB

Examiner

Marcela M. Cordero Garcia

Art Unit

1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 December 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-23 and 26 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-23 and 26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-8508)
Paper No(s)/Mail Date _____

- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Inventor's Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

This Office Action is in response to the replies received on 13 November 2007 and 21 December 2007.

Claims 1-23 and 26 are pending in the application.

Any rejection from the previous office action, which is not restated here, is withdrawn.

Applicant originally elected the species "the method of treating advanced prostate cancer comprising administration of an injectable solution of leuprolide, calcitriol and polysorbitan".

Claims 1-23 and 26 are presented for examination on the merits.

REJECTION MAINTAINED

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-4 and 16-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garnick et al. (US 5,780,435) in view of Beer et al. (Seminars in Oncology, August 2001) in further view of Lu et al. (US 5,284,657).

Garnick et al. teach administration of leuprolide in a sustained release formulation administered subcutaneously or intramuscularly (e.g., Examples 1-3) in order to treat advanced prostate cancer (e.g., claims 1-6, column 13, lines 24-26 and 45-56). The limitations "...injectable, sustained release depot formulation..." of claim 18 and "...single intramuscular injection per month of about 7.5 mg of leuprolide..." of claim 20 are taught, e.g., at Example 2, lines 58-62. The limitation of claim 17 is taught, e.g., at "...about 1 milligram per day..." is taught, e.g., at column 15, line 24, which teaches 0.01 mg/kg, which reads upon a 1 mg dose for a subject with 100 kg. The limitations "...daily.." in claim 17 and "weekly.." in claim 19, "...three months..." in claim 21, "four months..." in claim 22 and "...one-year.." are not expressly taught, however, the disclosure of Garnick et al. teaches that "...a therapeutically effective amount refers to an amount effective, at dosages and for periods of time necessary to achieve the desired result."" (e.g., column 15, lines 10-12). The limitations "...about 11.75 mg. In the form a three-month... formulation.", "...about 30 mg in the form of a four-month formulation" and "...about 65 mg in a form of a one-year implant" of claims 21, 22 and 23 are not expressly taught however, the disclosure of Garnick et al. teaches optimizing dosages for periods of time, depending on disease state, age and weight of the individual within 0.01 ug/kg-10mg/kg and preferably between about 0.01 to 5 mg/kg (e.g., column 15, lines 12-33). See also column 15, line 52, which teaches implants. The limitation "...isotonic.." of claim 17, is taught, e.g., at column 15, lines 34-36. The limitation "...saline..." of claim 17 is not expressly taught in Garnick et al.

Lu et al. is relied upon to teach the formula of leuprolide, which is 5-oxo-L-Pro-L-His-L-Trp-L-Ser-L-Tyr-D-Leu-L-Leu-L-Arg-Pro-N-ethylamide (e.g., column 3, lines 20-21, and Example 1) which reads upon the limitations of claims 2-4, wherein Xaa is D-Leu and Yaa is a modified proline residue (Pro-N-ethylamide, i.e., N-ethyl-L-prolinamide).

Garnick et al. and Lu et al. do not teach administering calcitriol with the leuprolide.

Beer et al. teach treating advanced prostate cancer (e.g., title of abstract) with a composition comprising calcitriol (lines 4-5). Beer et al. teach administering 0.5 ug/kg calcitriol orally (e.g., 60 kg patient: 30 ug).

It has been held that combinations of two or more compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is to be used for the very same purpose. In re Susi, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); In re Crockett, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (1960). As the court explained in Crockett, the idea of combining them flows logically from their having been individually taught in prior art. Therefore, since each of the reference teach that are effective in treating advanced prostate cancer, it would have been obvious to combine the two compounds with the expectation that such a combination would be effective in treating advanced prostate cancer. Thus, combining them flows logically from their having been individually taught in prior art. Please note that the combination above reads upon the limitation of claim 1: "... an amount of calcitriol sufficient to enhance the

effectiveness of luteinizing hormone releasing hormone agonist analog against the advanced prostate cancer relative to treatment with luteinizing hormone releasing hormone agonist analog alone... ". The adjustment of particular conventional working conditions (e.g., determining appropriate dosages and periods of administration, making isotonic saline solutions, within such method of treating advanced prostate cancer as taught by Garnick et al., column 15) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.

Applicant's arguments

Applicant argues that the secondary reference only describes the co-administration of calcitriol and docetaxel, paclitaxel and platinum compounds, Beer et al. contains no suggestion whatsoever that leuprolide or any other LHRH agonist analog should or could be substituted for docetaxel, paclitaxel or a platinum compound. The teachings of Garnick et al. have been mischaracterized as well. To treat prostate cancer, Garnick et al. teach the administration of LHRH-R antagonist prior to surgery. Leuprolide is not a LHRH-R antagonist, rather a LHRH-R agonist which is administered only after the treatment with a LHRH-R antagonist (Garnick et al. Examples 2-3). Nothing in Garnick et al would have led on of ordinary skill, whatever that skill level might have been to (1) ignore the express teachings of Garnick et al. vis-a-vis the use of LHRH-R antagonist and instead (2) administer calcitriol together with leuprolide. The conclusion is inescapable that the attempted combination of Garnick et al. and Beer et al. has been arrived at only by an impermissible hindsight reconstruction of the claimed

invention using applicant's own teachings as a guide. Lu et al. does not cure the defects of Garnick et al. as a reference against the present claims. The amino acid residue sequence of Leuprolide is not an issue here. Further, as also recognize by the Examiner, the express limitations of claims 17, 19, 21, 22 and 23 are not taught by Garnick et al. The level of ordinary skill in the pertinent art has not been resolved in this case, thus on the present record it cannot be resolved what limitations would or would not have been obvious to one of ordinary skill. The onus is on the Examiner to make a prima facie case of obviousness for the claimed invention. The Examiner has failed to do so, the rejection based on 35 USC 103 (a) must be withdrawn.

Response to arguments

Applicant's arguments have been carefully considered but not deemed persuasive because: (i) The rejection is under 103 and not under 102, therefore the references are not required to teach all the limitations at once; (ii) Beer et al. does not exclude (i.e., teach away from) combining calcitriol with leuprolide; (iii) The instant claims, as drafted, do not exclude use of LHRH-R antagonists, and/or define in any way steps regarding administration of active agents (e.g., before or after surgery); (iv) Lu et al. is simply relied upon to ascertain the sequence of Leuprolide and Examiner is in agreement that such sequence is not an issue here; (v) The level of ordinary skill in the art is set forth by the references provided within the rejection and for the reasons of record and those set forth above the rejection is maintained.

REJECTION MAINTAINED

Claims 1, 5-15 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garnick et al. (US 5,780,435) in view of Beer et al. (Seminars in Oncology, August 2001), Conway et al. (US 4,308,264) and Chen (US 6,919,370).

Garnick et al. and Beer et al. are relied upon as above. Beer et al. teach the limitation of claims 14-15: "...about 0.1 to about 20 ug/kg based on the weight of the patient" (e.g., administering 0.5 ug/kg calcitriol, which is about 30 ug in a 60 kg patient claim 11: "about 5 to about 30 ug of calcitriol".

Garnick et al. and Beer et al. do not teach solutions comprising 1 to about 30 micrograms of calcitriol with a polysorbitan (a non-ionic surfactant) such as polysorbate 20.

Conway et al. teach isotonic solutions comprising a saline medium, polysorbate 20, ascorbic acid and calcitriol (e.g., column 4, lines 8-14). The limitation of claim 5: "...isotonic..." is taught at claim 15. The limitation "...and a sufficient quantity of nonionic surfactant to solubilize the calcitriol therein" is taught at "column 4, lines 19-21. The limitation of claim 8 "...about 1 to about 15 mg/mL of ascorbic acid" is taught at column 5, lines 5-15. The limitation of claim 10: "... about 1 to about 2 mg/mL of EDTA" is taught e.g., at lines 8-10 in column 5. The limitation of claim 13: "...about 1 to about 10 mg/mL of polysorbitan" is taught e.g., at column 5, line 7. The limitation of claim 9: "about 2 to about 6 mg/mL of ascorbic acid" is not expressly taught.

Chen teaches solutions comprising saline polysorbate 20 and leuprolide (e.g., column 7, lines 16-23; column 8, lines 35-38). It also teaches adding therein

'osteoporosis agents' (e.g., column 7, line 59), such as calcitriol. The limitation of claim 26 "about 5 to about 20 milligrams per milliliter of polysorbate 20" is taught, e.g., at formulation 5, column 19 of Chen and column 5, line 7 and claim 12 of Conway et al.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Garnick et al. and Beer et al. by making injectable isotonic saline solutions of calcitriol comprising polysorbitan 20, ascorbic acid and EDTA as taught by Conway et al. and Chen. The skilled artisan would have been motivated to do so because Conway et al. teach therapeutic injections of isotonic saline calcitriol (e.g., column 2, lines 64-67) solutions comprising the excipients claimed (polysorbitan 20, EDTA and ascorbic acid). There would have been a reasonable expectation of success, given that Chen teaches combinations of all the main components (leuprolide, an osteoporosis agent such as calcitriol and polysorbate 20) in saline media injections for anti-cancer treatment. Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made. The adjustment of particular conventional working conditions (e.g., determining appropriate dosages and formulations within such advanced prostate cancer treatment method) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments

Garnick et al. and Beer et al. fail as references against claims 1, 5-15 and 26 for the same reasons as those advanced hereinabove. Additionally, as recognized by the examiner, the express limitation of 1 to about 30 micrograms of calcitriol with a polysorbitan as called for in claims 6, 7, 12 and 26 also is not taught. Likewise, the express limitation of 5 to 30 micrograms of calcitriol with a polysorbitan as called for in claims 12-13 is not taught. Neither Conway et al. nor Chen cure the foregoing defects of Garnick et al. and Beer et al. Conway et al. is clearly inapposite because it is directed to the treatment of neonatal hypocalcemia with an aqueous calcitriol solution. This has nothing to do with the presently claimed method for treating advanced prostate cancer. Chen is also inapposite vis-a-vis the present claims. Chen teaches solubilizer for paclitaxel (col. 7, line 8) and possibly leuprolide (col. 7, line 23) These solubilizers are PEG-Vitamin Es, quaternary ammonium salts, PEG-monoacid fatty esters, PEG-glycerol fatty esters, polysorbates, PEG_fatty alcohols (col. 7, lines 13-18; col. 14, line 67 to col. 15, line 3). Calcitriol is clearly not encompassed by the foregoing teaching, nor is calcitriol mentioned as an osteoporosis agent at col. 7, line 59, that can be solubilized using a paclitaxel solubilizer. By no stretch of the imagination does Chen teach a combination of leuprolide with calcitriol or a combination of leuprolide, calcitriol and polysorbate 20, much less the presently claimed method.

Response to Arguments

Applicant's arguments have been carefully considered but not deemed persuasive for the reasons set forth above, the reasons of record, and because (1)

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therapeutic aqueous solutions were known to be made containing aqueous calcitriol because Conway et al. teach therapeutic injections of isotonic saline calcitriol (e.g., column 2, lines 64-67) solutions comprising the excipients claimed (polysorbitan 20, EDTA and ascorbic acid). The adjustment of particular conventional working conditions (e.g., determining appropriate amounts of calcitriol and leuprolide within such compositions used for a therapeutic method) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. As such, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g., appropriate amounts, excipients and solubilizers), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2145.05). One would have been motivated to determine all optimum and operable conditions in order to achieve the most effective and safest method in the most efficient manner. One would have had a reasonable expectation for success because such modifications are routinely determined and optimized in the art through routine experimentation.

It has been held that under KSR that "obvious to try" may be an appropriate test under 103. The Supreme Court stated in KSR:

When there is motivation "to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill

and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, ___, 82 USPQ2d 1385, 1397 (2007).

The "problem" facing those in the art was the treatment of advanced prostate cancer, and there were a limited number of methodologies available to do so such as those of Beer et al. and Garlick et al. The skilled artisan would have had reason to try these methodologies with the reasonable expectation that at least one would be successful. In the instant case the two compounds: leuprolide and calcitriol were taught by the prior art as useful for treating advanced prostate cancer as set forth above. Thus, treating advanced prostate cancer with these compounds and optimizing their administration by determining effective amounts of active agents and appropriate solvents, excipients and solubilizers is not a "the product not of innovation but of ordinary skill and common sense," leading to the conclusion that invention is not patentable as it would have been obvious.

In addition, KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness.

See the recent Board decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Patt. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2s at 1396) (available at <http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf>).

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M. Cordero Garcia whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 7:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marcela M Cordero Garcia/
Examiner, Art Unit 1654

MMCG 03/08

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654